Definition of the residue (for compliance with the MRL and for estimation of dietary intake for animal commodities): *Sum of flupyradifurone and difluoroacetic acid (DFA), expressed as parent equivalents*

The residue is not fat soluble

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The 2015 JMPR established an ADI of 0–0.08 mg/kg bw for flupyradifurone. The International Estimated Daily Intakes (IEDIs) of flupyradifurone were calculated for the 17 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current and previous Meetings. The results are shown in Annex 3 of the 2017 JMPR report. The calculated IEDIs were 6–20% of the maximum ADI. The Meeting concluded, on the basis of the information provided to the current and previous Meetings, that the long-term dietary exposure to residues of flupyradifurone is unlikely to present a public health concern.

Short-term dietary exposure

The 2015 JMPR established an ARfD of 0.2 mg/kg bw for flupyradifurone. The International Estimated Short Term Intakes (IESTIs) of flupyradifurone were calculated for food commodities using the HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting. The results are shown in Annex 4 in the 2017 JMPR report. The IESTIs were 10% of the ARfD for the general population and 30% of the ARfD for children. The Meeting concluded that the short-term dietary exposure to residues of flupyradifurone, resulting from the uses considered by the Meeting, are unlikely to present a public health concern.

5.19 FOSETYL-ALUMINIUM (302)

TOXICOLOGY

Fosetyl-aluminium (fosetyl-Al) is the ISO-approved common name for aluminium ethyl hydrogen phosphonate, with the CAS number 39148-24-8. Fosetyl-Al belongs to a group of the phosphonate class of compounds used as fungicides and bactericides. Phosphonates disrupt phosphorus metabolism and interrupt the synthesis of complex molecules and specific enzymes by the targeted pathogen. Fosetyl-Al is used as a protectant on a variety of crops including vines, fruits (citrus, pineapples, avocados, berries, stone and pome fruit), vegetables and salads and hops.

Fosetyl-Al has not been previously evaluated by the JMPR and was reviewed by the present Meeting at the request of the CCPR.

Some of the critical studies do not comply with GLP or OECD test guidelines or other validated guidelines because the data were generated before the implementation of these guidelines. The studies were considered adequate for the evaluation.

Biochemical aspects

Following oral administration to rats at doses of 100–3000 mg/kg bw, ^{14}C-labelled fosetyl-Al was almost completely absorbed and almost completely eliminated in urine, faeces and exhaled air within 24 hours. There was no evidence of accumulation. Fosetyl-Al is metabolized to ethanol, acetic acid, carbon dioxide and phosphonic acid (referred to as phosphonate). The phosphonate is excreted predominantly in the urine (equivalent to 73% of the administered compound) together with unchanged material (26–28% of the administered compound).

Toxicological data

The acute toxicity of fosetyl-Al was studied after oral administration in mice, rats and rabbits (LD_{50} > 2000 mg/kg bw), dermal administration in rats (LD_{50} > 2000 mg/kg bw) and inhalation in rats (LC_{50} > 5.11 mg/L). Fosetyl-Al was not irritating to the skin of rabbits but produced moderate to severe ocular irritation in rabbits. Fosetyl-Al was not sensitizing in guinea-pigs.

In short-term studies of toxicity in different species, the most notable effects were seen in the bladder, ureters and kidneys of rats exposed to high doses of fosetyl-Al. In contrast, fosetyl-Al exhibited low toxicity in rat oral toxicity studies at doses less than the limit dose (1000 mg/kg bw per day).

In the first available short-term study, rats were administered fosetyl-Al at dietary concentrations of 0, 1000, 5000 or 25 000 ppm for 3 months (equal to 0, 75.2, 366 and 1920 mg/kg bw per day for males or 0, 98.0, 480 and 2500 mg/kg bw per day for females, respectively). A slight increase in the incidence of extramedullary haematopoiesis was observed in the spleen of high dose rats, but there were no corresponding effects on haematology or spleen weight changes. The NOAEL was 25 000 ppm (equal to 1920 mg/kg bw per day).

Another short-term dietary toxicity study in rats examined the effects of fosetyl-Al at 0, 8000, 30 000 and 50 000 ppm (equal to intakes of 0, 544, 2130 and 3500 mg/kg bw per day for males and 0, 648, 2400 and 4300 mg/kg bw per day for females, respectively) after exposure durations of 2–13 weeks and recovery periods of 8–16 weeks. The NOAEL was 8000 ppm (equal to 544 mg/kg bw per day) based on histopathological changes in the kidney, impairment of calcium/phosphorous metabolism, calculi and hyperplasia in the urinary bladder observed at 30 000 ppm (equal to 2130 mg/kg bw per day).

In a subsequent 90-day toxicity study, rats were administered fosetyl-Al in the diet at 0, 2000, 6000 or 20 000 ppm (equal to 0, 128, 383 or 1270 mg/kg bw per day for males and 0, 155, 455 or 1580 mg/kg bw per day for females, respectively). There were two treatment-related deaths at 20 000 ppm (equal to 1270 mg/kg bw per day). The NOAEL was 6000 ppm (equal to 383 mg/kg bw per day).

In the final 90-day toxicity study, rats were administered 0, 2000, 6000 or 20 000 ppm fosetyl-Al in the diet (equal to 0, 118, 363 and 1230 mg/kg bw day for males and 0, 148, 446 and 1430 mg/kg bw per day for females, respectively). No treatment-related effects were observed. The NOAEL was 20 000 ppm (equal to 1230 mg/kg bw per day), the highest dose tested.

In a 3-month study of toxicity in dogs, fosetyl-Al was administered in the diet at 0, 2000, 10 000 or 50 000 ppm (equal to 0, 58, 274 and 1310 mg/kg bw per day for males and 0, 58, 272 and 1450 mg/kg bw per day for females, respectively). No treatment-related effects were observed. The NOAEL was 50 000 ppm (equal to 1310 mg/kg bw per day), the highest dose tested.

In a 2-year toxicity study in dogs, fosetyl-Al was administered in the diet at 0, 10 000, 20 000 or 40 000 ppm (equal to 0, 309, 609 and 1230 mg/kg bw per day for males or 0, 288, 632 and 1190 mg/kg bw per day for females, respectively). The NOAEL was 10 000 ppm (equal to 309 mg/kg bw per day) based on testicular degeneration observed at 20 000 ppm (equal to 609 mg/kg bw per day). No other treatment-related effects were observed.

In a 24-month carcinogenicity study, mice were administered fosetyl-Al in the diet at 0, 2500, 10 000 or 30 000 ppm (equal to 0, 352, 1410 and 3960 mg/kg bw per day for males and 0, 409, 1670 and 4550 mg/kg bw per day for females, respectively). There were no treatment-related effects on the incidence of neoplasia or on systemic toxicity end-points. The NOAEL for general toxicity and carcinogenicity was 30 000 ppm (equal to 3960 mg/kg bw per day), the highest dose tested.

In a 24-month carcinogenicity study in rats, fosetyl-Al was administered in the diet at 0, 2000, 8000 or 30 000 ppm (equal to 0, 88, 348 and 1370 mg/kg bw per day for males and 0, 117, 450 and 1790 mg/kg bw per day for females, respectively). Fosetyl-Al exposure resulted in increased incidence of uroliths and mineralization in the urinary bladder, and inflammation, hyperplasia and neoplasia (transitional cell carcinoma) in the urinary transitional epithelium at doses of 30 000 ppm (equal to 1370 mg/kg bw per day). The NOAEL was 8000 ppm (equal to 348 mg/kg bw per day).

The Meeting concluded that fosetyl-Al is carcinogenic in rats but not in mice.

Fosetyl-Al was tested for genotoxicity in an adequate range of in vitro and in vivo assays. No evidence of genotoxicity was found.

The Meeting concluded that fosetyl-Al is unlikely to be genotoxic.

The carcinogenicity in rats was related to the exceedingly high dose administered, resulting in precipitation in the urinary tract. The Meeting concluded that the toxicological data and physical chemistry associated with fosetyl-Al support the following mode of action: Fosetyl-Al at high doses (>1000 mg/kg bw per day) results in precipitation of calcium phosphonate or calcium phosphate and formation of uroliths in the urine. These uroliths cause sustained irritation, inflammation and cytotoxicity to urothelial cells and induce regenerative urothelial hyperplasia that progresses to transitional cell carcinomas, particularly in the bladder and kidney. Further, this carcinogenic mode of action only occurs at doses high enough to cause calcium phosphate or calcium phosphonate precipitation in urine. Human exposure levels will not approach the solubility limit of calcium phosphate or calcium phosphonate. Therefore, fosetyl-Al is unlikely to pose a carcinogenic risk to humans from the diet.

In a three-generation study of reproductive toxicity in rats, fosetyl-Al was administered in the diet at 0, 6000, 12 000 or 24 000 ppm (equal to 0, 482, 954 and 1960 mg/kg bw per day for males and 0, 553, 1060 and 2130 mg/kg bw per day for females, respectively). The NOAEL for parental toxicity was 6000 ppm (equal to 482 mg/kg bw per day) based on reduced body weights at 12 000 ppm (equal to 954 mg/kg bw per day). The NOAEL for offspring toxicity was 6000 ppm (equal to 482 mg/kg bw per day) based on reduced pup weight during lactation at 12 000 ppm (equal to 954 mg/kg bw per day). The NOAEL for reproductive effects was 24 000 ppm (equal to 1960 mg/kg bw per day), the highest dose tested.

In a study of developmental toxicity, rats were dosed by oral gavage at 0, 500, 1000 or 4000 mg/kg bw per day on gestation days 6–15. The NOAEL for maternal toxicity was 1000 mg/kg bw per day based on mortality and markedly reduced body weight gain at 4000 mg/kg bw per day.

The NOAEL for embryo/fetal toxicity was 1000 mg/kg bw per day based on reduced litter weight, lower mean fetal weight, increased incidence of major malformations (fused rib, hydrocephaly, transposed aortic arch) and minor visceral and skeletal anomalies at 4000 mg/kg bw per day. The fetal effects were seen at a dose associated with maternal lethality that is above the recommended limit dose for this study type; thus, the effects are considered not indicative of specific developmental toxicity.

In a rabbit developmental toxicity study, animals were dosed by gavage at 0, 50, 100 or 300 mg/kg bw per day. The NOAEL for maternal toxicity was 100 mg/kg bw per day based on one maternal death on gestation day 27 at 300 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 100 mg/kg bw per day based on increased incidence of distended (dilated) ureters in fetuses at 300 mg/kg bw per day. No malformations were observed.

The Meeting concluded that fosetyl-Al was not teratogenic in rabbits; fosetyl-Al was teratogenic in the rat only when tested at excessive dose levels that induced severe maternal toxicity.

Fosetyl-Al did not produce delayed neuropathy in an acute study in hens dosed at 2000 mg/kg bw.

None of the neurological end-points included in the short-term toxicity studies, including an acetylcholinesterase assay, demonstrated evidence of neurotoxicity.

The Meeting concluded that fosetyl-Al was not neurotoxic and did not induce delayed neuropathy.

Toxicological data on metabolites and/or degradates

The main metabolite of fosetyl-Al, phosphonic acid, was tested in biochemical studies, short-term toxicity studies, a chronic toxicity study in rats and genotoxicity studies as either the free acid or the sodium or potassium salts.

Sodium [^{32}P]phosphonate was extensively absorbed and rapidly excreted, largely unchanged. The majority (59–65%) of labelled substance was excreted unchanged in urine, and 30–32% of the labelled substance was excreted in faeces. Up to 35% of the radiolabel excreted in faeces was identified as ^{32}P-labelled phosphate; the remainder of the radiolabel in faeces was associated with ^{32}P-labelled phosphonate. Overall conversion to phosphate was around 10% of the administered dose.

Phosphonic acid or its sodium or potassium salts exhibited low acute oral toxicity in rats and mice ($LD_{50} \geq 1600$ mg/kg bw), inhalation toxicity in rats ($LC_{50} > 6.14$ mg/L) and dermal toxicity in rabbits ($LD_{50} > 2000$ mg/kg bw). Phosphonic acid was not irritating to the skin of rabbits and was slightly irritating to the eyes of rabbits.

In a 3-month toxicity study in rats, monosodium phosphonate was administered in the diet at 0, 2500, 5000 or 25 000 ppm (equal to 0, 100, 200 and 1200 mg/kg bw per day for males and 0, 100, 300 and 1600 mg/kg bw per day for females, respectively, expressed as phosphonic acid). Diarrhoea, increased water consumption, lower urinary pH and increased urinary sodium and calcium excretion were observed at 25 000 ppm (equal to 1200 mg/kg bw per day phosphonic acid). The NOAEL was 5000 ppm (equal to 200 mg/kg bw per day phosphonic acid).

In a 27-month chronic toxicity and carcinogenicity study in rats, monosodium phosphonate was administered in the diet at 0, 2000, 8000 or 32 000 ppm (equal to 0, 83.9, 348 and 1480 mg/kg bw per day for males and 0, 104, 434 and 1820 mg/kg bw per day for females, respectively). Soft stools, decreased body weight, decreased food efficiency, decreased urine pH and increased relative kidney weight were observed at 32 000 ppm (equal to 1480 mg/kg bw per day sodium phosphonate or 1160 mg/kg bw per day when expressed as phosphonic acid). The NOAEL was 8000 ppm (equal to 348 mg/kg bw per day sodium phosphonate or 274 mg/kg per day when expressed as phosphonic acid). There was no evidence of increased neoplasia in treated animals.

Phosphonic acid or its sodium salt tested negative for genotoxicity in bacteriophage induction, bacterial reverse mutation and in vivo mouse micronucleus assays.

Human data

In reports on manufacturing plant personnel, no adverse health effects were noted. No information on accidental or intentional poisoning in humans was available.

The Meeting concluded that the existing database on fosetyl-Al was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI for fosetyl-Al of 0–1 mg/kg bw based on the NOAEL of 100 mg/kg bw per day for maternal and embryo/fetal toxicity from the rabbit developmental toxicity study. A safety factor of 100 was applied.

The Meeting concluded that it was not necessary to establish an ARfD for fosetyl-Al in view of its low acute oral toxicity and the absence of embryo/fetal toxicity and any other toxicological effects that would be likely to be elicited by a single dose. An increase in malformations in a rat developmental study was seen at 4000 mg/kg bw per day, with a NOAEL of 1000 mg/kg bw per day, which is above the trigger level used by the JMPR for ARfDs. No effects were seen at the beginning of dosing in the rabbit developmental study and the effects on fetuses (dilated ureter) are considered unrelated to a single dose.

Phosphonic acid, the major metabolite, is toxicologically similar to the parent and was considered to be covered by the ADI of fosetyl-Al.

A toxicological monograph was prepared.

Levels potentially relevant to risk assessment of fosetyl-Al

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	30 000 ppm, equal to 3 960 mg/kg bw per day[b]	–
		Carcinogenicity	30 000 ppm, equal to 3 960 mg/kg bw per day[b]	–
Rat	Two-year studies of toxicity and carcinogenicity[a]	Toxicity	8 000 ppm, equal to 348 mg/kg bw per day	30 000 ppm, equal to 1 370 mg/kg bw per day
		Carcinogenicity	8 000 ppm, equal to 348 mg/kg bw per day	30 000 ppm, equal to 1 370 mg/kg bw per day
	Three-generation study of reproductive toxicity[a]	Reproductive toxicity	24 000 ppm, equal to 1 960 mg/kg bw per day[b]	–
		Parental toxicity	6 000 ppm, equal to 482 mg/kg bw per day	12 000 ppm, equal to 954 mg/kg bw per day
		Offspring toxicity	6 000 ppm, equal to 482 mg/kg bw per day	12 000 ppm, equal to 954 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	1 000 mg/kg bw per day	4 000 mg/kg bw per day
		Embryo/fetal toxicity	1 000 mg/kg bw per day	4 000 mg/kg bw per day
Rabbit	Developmental toxicity study[c]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day

		Embryo/fetal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
Dog	Three-month study[a]	Toxicity	50 000 ppm, equal to 1 310 mg/kg bw per day[b]	–
	Two-year study[a]	Toxicity	10 000 ppm, equal to 309 mg/kg bw per day	20 000 ppm, equal to 609 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

Acceptable daily intake (ADI; applies to fosetyl-Al and phosphonic acid)

0–1 mg/kg bw per day fosetyl-Al

Estimate of acute reference dose (ARfD)

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to fosetyl-Al

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; >90%
Dermal absorption	No data
Distribution	Widespread: highest concentrations in fat, adrenals, skin, fur, testes and kidneys
Potential for accumulation	Low
Rate and extent of excretion	Rapid: Largely complete by 24 h; primarily via urine
Metabolism in animals	Converted to ethanol, acetic acid, carbon dioxide and phosphonic acid
Toxicologically significant compounds in animals, plants and the environment	Fosetyl-Al, phosphonic acid
Acute toxicity	
Rat, LD_{50}, oral	5 250 mg/kg bw
Rat, LD_{50}, dermal	>2 000 mg/kg bw
Rat, LC_{50}, inhalation	>5.11 mg/L
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Moderately irritating
Guinea-pig, dermal sensitization	Non-sensitizing (Magnusson–Kligman)
Repeated-dose studies of toxicity	
Target/critical effect	Urinary bladder and kidney/histopathological changes, impairment of calcium/phosphorous metabolism, calculi and hyperplasia

Lowest relevant oral NOAEL	544 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Urinary bladder/hyperplasia and neoplasia of the urinary transitional epithelium
Lowest relevant NOAEL	348 mg/kg bw per day (rat)
Carcinogenicity	Carcinogenic in rats but not in mice[a]
Genotoxicity	
	Unlikely to be genotoxic[a]
Reproductive toxicity	
Target/critical effect	No reproductive effect
Lowest relevant parental NOAEL	482 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	482 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	954 mg/kg bw per day (rat)
Developmental toxicity	
Target/critical effect	Ureter/dilated ureter
Lowest relevant maternal NOAEL	100 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	100 mg/kg bw per day (rabbit)
Other toxicological studies	
Phosphonic acid and its sodium or potassium salts	Excreted in urine (59–65%) and faeces (30–32%)
	Oral $LD_{50} \geq 2\ 400$ mg/kg bw (rat), 1 600 mg/kg bw (mouse)
	90-day rat: NOAEL 200 mg/kg bw per day, expressed as phosphonic acid
	27-month chronic toxicity rat: NOAEL 274 mg/kg bw per day, expressed as phosphonic acid
	Negative in genetic toxicity assays [a]
	No evidence of carcinogenicity[a]
Human data	
	None identified

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

Compound		Value	Study	Safety factor
Fosetyl-Al[a]	ADI	0–1 mg/kg bw	Rabbit developmental toxicity	100
	ARfD	Unnecessary		

[a] Applies to fosetyl-Al and phosphonic acid, expressed as fosetyl-Al.

[Also see PHOSPHONIC ACID (301)]

RESIDUE AND ANALYTICAL ASPECTS

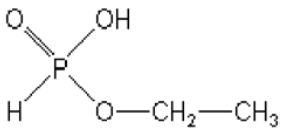
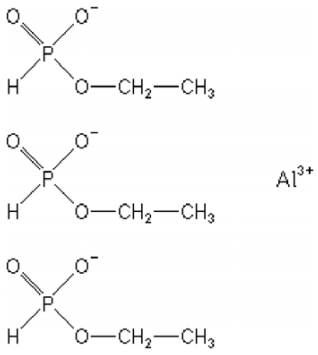
Fosetyl-aluminium (fosetyl-Al), fosetyl and phosphonic acid are systemic fungicides with protectant action against a number of oomycete and ascomycete fungi and some plant pathogenic bacteria in a range of fruit, vegetables and ornamental crops. They are rapidly absorbed through both leaves and roots and exhibit both acropetal and basipetal translocation. Their mode of action is by inhibiting germination of spores and by blocking development of mycelium, competing with phosphate as allosteric regulator of several enzymes.

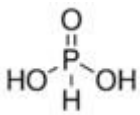
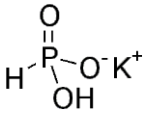
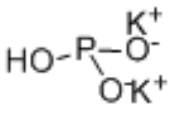
Fosetyl-Al and phosphonic acid were scheduled by the 48th Session of the CCPR as new compounds for consideration by the 2017 JMPR. The Meeting received information and studies on metabolism, analytical methods, supervised field trials, processing, freezer storage stability and environmental fate in soil for fosetyl, fosetyl-Al and phosphonic acid.

Authorisations exist in many countries for the use of fosetyl and fosetyl-Al as pre-plant dips, foliar, drench or drip-irrigation treatments and authorisations also exist for phosphonic acid (formulated as potassium, sodium and ammonium salts) in a number of countries for use as trunk injections, pre-plant dips, foliar, soil and post-harvest treatments.

In biological systems, since fosetyl, fosetyl-Al and the phosphonic acid are closely related, the Meeting agreed to evaluate the three compounds together and that the conclusions in this Appraisal would cover fosetyl and its salts as well as phosphonic acid and its salts.

Fosetyl-Al has been evaluated by the Joint FAO/WHO Meeting on Pesticide Specifications (JMPS). Specifications, published in 2013 and available at http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/en/.

Fosetyl	Fosetyl-Al
	
MW 110	MW 354.1

Phosphonic acid	Potassium hydrogen phosphonate	Dipotassium phosphonate
		
MW 82	MW 120	MW 158

Plant metabolism

The Meeting received plant metabolism studies on citrus, apple, grape leaves, pineapple and tomato following foliar applications of labelled and unlabelled fosetyl-Al and on pineapple (pre-plant dip) and tomato (hydroponic) treatments of fosetyl-Al and phosphonic acid.

Fosetyl-Al

Citrus– foliar applications

In a study on outdoor pot-grown tangerine and orange trees, three (tangerine) or four (orange) ^{14}C-fosetyl-Al treatments of 0.066 g ai/tree were applied with a paint brush to all aerial parts of the trees at 1–2 month intervals between the end of flowering and two months before harvest. Total application rates were 0.2 g ai/tree (tangerines) and 0.26 g ai/tree (oranges).

Total radioactive residues were 2.8 mg ai/kg in oranges and 1.2 mg ai/kg in mandarins. Residues were extracted twice with water, then with acetone, and finally with acidified methanol. Most of the extracted residue was found in the aqueous extracts, 66–68% TRR in whole fruit and 90-93% TRR in juice. About 46–50% TRR in whole fruit was present as glucose, with fosetyl-Al accounting for about 5–12% TRR. In juice, fosetyl-Al residues were about 8–18% TRR with glucose being the predominant component (70–75% TRR).

Apples– foliar applications

In a study on the distribution and composition of ^{14}C-fosetyl-Al in apples, one branch of an outdoor apple tree (fruit and leaves) was treated with two sprays of 0.2 g ai/branch, 7 days apart and fruit and leaves were sampled before and after each application and again 7 and 14 days after the second treatment. Fruit and leaves were washed with deionised water and peel/flesh samples were extracted by refluxing in acidified acetonitrile/water.

Most of the radioactive residues in leaves were found in the surface wash, 96% TRR decreasing to 66% TRR at the end of the 21-day study period. Surface residues of the apple fruits predominated during the first 7 days (89% TRR), but subsequently penetrated into the fruit (53-58% TRR), mostly in the peel (39% TRR 14 days after the 2nd application).

Fosetyl-Al was the predominant residue in the fruit surface washes, initially 93% of TRR, decreasing to 41% TRR 14 days after the second application. Very small amounts of fosetyl-Al were detectable in peel and flesh (≤ 1.7% TRR).

The major radioactive metabolite identified in both apple fruit and leaves was ^{14}C-ethanol, present as a surface residue from day 0 (4.4% TRR in fruit and 28% TRR in leaves). ^{14}C-ethanol residues increased to about 50% TRR in fruit and 26% TRR in leaves.

Grape leaves – foliar treatment

Individual leaves from one grape vine (pruned to a single 1.2 metre shoot) grown in a glasshouse were treated with 0.76 mg of ^{14}C-fosetyl-Al for autoradiography. Leaves from a different vine (pruned to a single 1 metre shoot) grown in a glasshouse were treated with 4.5-9 mg of ^{14}C-fosetyl-Al for studying metabolism. Leaves were harvested at intervals up to 14 days after treatment, washed or soaked for 15 minutes in water (with added non-ionic surfactant) and the radioactive residues in the washings was determined by liquid scintillation counting (LSC). Autoradiography involved exposure to X-ray film for two weeks.

Autoradiography showed that radioactive residues moved from the treated leaves to the shoot apex (upper border of the leaves) with uptake being greater in younger leaves. Most of radiolabelled fosetyl-Al applied to vine leaves remained on the leaf surface (recovered in the wash), with limited translocation to untreated parts of the plant or to new growth. The major metabolic product found in treated and untreated plant parts was phosphonic acid.

Pineapple – dip/foliar treatments

In a two-part study on pineapple, ^{14}C-fosetyl-Al was applied as a pre-plant crown dip, followed a year later by foliar application of ^{14}C-fosetyl-Al. Whole plants were sampled at intervals up to harvest (480 days after the dip treatment) and samples from the combined pre-plant dip+foliar spray treatment were also sampled immediately after the spray treatment (day 365) and at harvest, 122 days later (487 days after the dip treatment).

Total radioactivity in the aerial parts of the pre-plant dip-treated plants decreased considerably over the study period, unextracted radioactivity increased steadily in the aerial plant parts and total radioactivity in the roots increased to 6.8% AR in the whole plant at harvest. Mature fruit at harvest contained negligible quantities of radioactive residues, 0.38% AR following the pre-plant dip treatment and 1.1% AR following the combined pre-plant dip+foliar spray treatment.

Tomato – foliar applications

In a study on tomato, two applications of ^{14}C-fosetyl-Al were made 14 days apart to fruit, leaves and stems of outdoor, sheltered tomato plants at a rate equivalent to 4.5 kg ai/ha, and samples of fruit were taken 2 hours and 14 hours after the first treatment and then 14 days and 42 days after the second treatment (42 DALA). Fruit were washed in water and subsequently blended and separated into juice and solids.

In whole tomatoes, about 98% TRR (1.4 mg ai eq/kg) was found in the 2-hour wash, with about 12% TRR (0.34 mg ai eq/kg) being removed in the 42 DALA fruit wash. Initial radioactivity in the liquid and solid fractions (3-4% TRR) increased to about 38% TRR (liquid fraction) and 50% TRR (tomato solids).

In the tomato wash, ^{14}C-fosetyl-Al initially accounted for about 77% TRR, decreasing to about 10% TRR in the 42 DALA samples. A similar pattern was observed in whole fruit, with parent decreasing from 80% TRR to about 3% TRR. Conversely, fosetyl-Al was a minor component of the radioactivity in tomato juice and extracted solids, increasing from about 3% TRR to 16% TRR in juice and from 0% TRR to 4% TRR in the solids.

Significant metabolites in whole fruit were ^{14}C-ethanol, making up about 15% TRR 2 hours after the first application, decreasing to about 12% TRR after 14 days. In the 14 DALA samples, ^{14}C-glucose was present at about 9.5% TRR, increasing to about 16% TRR in 48 DALA samples. Other radiolabelled components in the tomato solids fraction included ^{14}C-cellulose, ^{14}C-lignin and ^{14}C-starch.

Tomato – soil, petiole, leaf applications (supplementary study)

In a study using unlabelled fosetyl-Al or phosphonic acid, to investigate the distribution of residues in tomatoes, plants were treated with 0.16 or 0.32 g ai/plant by soil watering; with 7.2 mg ai fosetyl-Al/plant or 5 mg ai phosphonic acid per plant as a petiole application or with 0.4 g ai/L fosetyl-Al as a partial leaf spray. Treated and untreated stems, petioles and leaves were analysed for fosetyl-Al and phosphonic acid.

In the soil watering experiment, residues of fosetyl-Al were only found in stem/petioles 1–2 hours after treatment, with residues of phosphonic acid increasing rapidly in leaves and stems/petioles within 1 hour of watering, reaching a plateau in stems/petioles after 7 days and continuing to increase in leaves at the end of the 14-day study period.

In the petiole absorption experiment, residues of fosetyl-Al were found in stems, petioles and leaves above and below the treated petiole, with no trend of degradation. In contrast, in the phosphonic acid treated plants, higher residues were found in upper plant parts (in stem, petioles and leaves) as well as in the lower leaves, indicating translocation in both directions, but preferentially migration towards the apex (acropetal).

In the foliar treatment experiment, residues of fosetyl-Al were found at similar levels in the untreated plant parts (stems, petioles and leaves) above and below the treated leaves. Residues of phosphonic acid were also found in the untreated plant parts, peaking in the 8-hour leaf samples.

Tomato – hydroponic applications (supplementary study)

Hydroponically grown tomato plants (with 5 mature leaves) were treated with unlabelled fosetyl-Al by dipping the root systems in a solution of 2.26 mM fosetyl-Al for either 1 hour or 3 hours. Samples of roots, leaves, internodes and growing tips were analysed for fosetyl and phosphonic acid.

Fosetyl-Al was taken up by the roots and distributed through the plants within 1–3 hours and hydrolysed to phosphonic acid. After 3 days, residues of fosetyl were not found above trace levels in any aerial parts, with minor amounts found in roots. Phosphonic acid residues were found in all plant parts, increasing in young leaves and buds over the 3-day study period.

In summary, fosetyl-Al metabolism involves dissociation to fosetyl and conversion to O-ethyl phosphonate, the hydrolysis of the ethyl ester bond to form phosphonic acid and ethanol, the latter being either volatilised or incorporated into natural products. Fosetyl-Al and especially phosphonic acid are readily absorbed in plants and able to migrate in both directions, with phosphonic acid tending to migrate preferentially towards the growing tips.

Phosphonic acid

In addition to the studies conducted with fosetyl-Al (where the distribution and fate of phosphonic acid were investigated), a number of published papers were available on the behaviour of phosphonic acid in plants. Generally, phosphonic acid is rapidly (within minutes) absorbed by plant leaves or roots and translocated in both xylem and phloem, moving to sinks with the greatest demand for nutrients. Phosphonic acid is not readily oxidised to phosphate in plants.

Environmental fate

The Meeting received information on the environmental fate and behaviour of fosetyl-Al and phosphonic acid, including hydrolytic stability, photochemical degradation in soils and aerobic metabolism studies.

Hydrolysis

Fosetyl (and fosetyl-Al) dissociate in water to form O-ethyl phosphonate (and aluminium ions), with the O-ethyl phosphonate hydrolysing in biological systems to phosphonic acid by microbial activity. Phosphonic acid is not likely to occur in biological systems as the free acid under physiological and environmental conditions (pH 4 to 9), spontaneously forming salts in contact with soil or natural water with any suitable counter ion present (i.e. sodium, potassium, magnesium, calcium).

Both fosetyl-Al and phosphonic acid were stable for at least 30 days in sterile buffered solutions at pH levels reflecting those in biological systems (pH 5 to 9).

Aerobic soil metabolism

Fosetyl-Al

Aerobic degradation of fosetyl-Al was investigated in ten different soils (16 hours to 120 days in the dark at 20 °C or up to 64 days at 12 °C). Degradation was rapid, with DT_{50} values of 15–90 minutes. The proposed degradation pathway involves dissociation to O-ethyl phosphonate, the hydrolysis of the ethyl ester bond to form phosphonic acid (attributed to microbiological activity) and ethanol, the latter being either released as CO_2 or incorporated into soil organic matter as bound residues. Fosetyl-Al (and fosetyl) can be classified as non-persistent. The predominant degradate is phosphonic acid.

Phosphonic acid

Aerobic degradation of phosphonic acid was investigated in seven different soils (16–17 weeks in the dark at 20–28 °C). The studies generally reported a steady decline, attributed to soil reactions or to microbial transformation to phosphate. Calculated DT_{50} values ranged from 28–219 days. Phosphonic acid can be classified as moderately persistent to persistent.

Photochemical degradation in soil

Fosetyl-Al

No fosetyl-Al photolysis studies were conducted because of the rapid aerobic soil degradation and the lack of significant light absorption at wavelengths of more than 290 nm.

Phosphonic acid

The photolytic degradation of phosphonic acid in soil was investigated in two studies, involving treated soil surface irradiation for intervals up to 21 days and 45 days. Extractable residues of phosphonic acid decreased slowly over time, this being attributed to reactions with hydroxyl or peroxy radicals formed in irradiated soil components. The lack of significant light absorption at wavelengths of more than 200 nm provides support for this indirect photolytic effect. Residues degraded to about half the initial concentrations after about 21 days in the two studies.

Rotational crops

Fosetyl

In four rotational crop field trials involving total application rates equivalent to 2.3 kg ai fosetyl/ha to lettuce as the primary crop, carrots, lettuce and wheat or barley were planted as rotational crops, at plant-back intervals of 26–46 days. In mature carrot roots and tops, lettuce, wheat/barley forage, fodder and grain, total residues of fosetyl plus phosphonic acid were all below the phosphonic acid LOQs of 0.1 mg/kg (0.5 mg/kg for cereal forage and fodder). The one exception was a phosphonic acid residue of 0.21 mg/kg in one sample of grain.

Based on the results for the combined residues of fosetyl and phosphonic acid in these studies, and on the short soil half-life for fosetyl, residues of fosetyl (and fosetyl-Al) are not expected in rotational crops.

Phosphonic acid

In a rotational crop study involving a total (bare soil) application rate equivalent to 10 kg ai phosphonic acid/ha, residues of phosphonic acid were measured in radish roots and tops, lettuce and barley fodder and grain from crops planted 32 days after treatment and also in radish roots and tops from plants sown 182 days after treatment.

In the 32-day PBI crops, average phosphonic acid residues of 0.58–1.1 mg/kg were found in radish roots and 0.67–1.0 mg/kg in lettuce leaves. Residues below the LOQ of 0.5 mg/kg were detected in the 32-day PBI radish leaves, barley fodder and grain. Only low levels remained in the radish roots and leaves from plants sown 6 months after treatment, (estimated levels of 0.03 mg/kg and 0.09 mg/kg respectively).

Taking into account the results from the rotational crop studies for fosetyl and phosphonic acid, residues of phosphonic acid are not expected in rotational crops at levels above 0.5 mg/kg, especially at PBIs longer than 30 days.

Animal metabolism

Fosetyl-Al

The Meeting received animal metabolism studies on rats and lactating goats where animals were dosed with fosetyl-Al radiolabelled in the 1-C position.

In rats, the metabolism of fosetyl-Al and phosphonic acid was reviewed in the framework of the toxicological evaluation by the current Meeting

Following oral administration to rats, ^{14}C-fosetyl-Al was almost completely absorbed and almost completely eliminated in exhaled air, urine, and faeces within 24 hours. Fosetyl-Al undergoes

extensive hydrolysis *in vivo* to give ethanol and phosphonate. The phosphonate is excreted predominately in the urine (equivalent to 73% of the administered compound) together with unchanged material (26–28% of the administered compound).

In a lactating goat study, two animals were orally dosed for 7 days with ^{14}C-fosetyl-Al at doses equivalent to 10.5 ppm in the diet (21 mg/goat/day) with an additional goat being dosed for three days with 10.5 ppm in the diet and used in the CO_2 trapping chamber. All goats were sacrificed 24 hours after the 7th daily dose and various tissue samples were taken for analysis. Average LOQs for the different sample types were 0.0014 mg ai eq/kg in milk and 0.0026 to 0.0032 mg ai eq/kg in all tissues.

About 13% of the total dose was excreted with urine and about 5% in faeces. In expired air, $^{14}CO_2$ was not detected within the first 30 minutes but increased over the 3-day study period to 24% of the daily dose and in total, made up 17.5% of the administered dose.

In milk, residues reached a plateau after 3 days (about 2 mg ai eq/kg–17% AD). In tissues, less than 1.0% of the administered dose was found in liver and kidney, up to 2.2% AD in fat and up to 1% AD in muscle. Highest concentrations of radioactive residues in the two goats were in liver (0.49-0.57 mg ai eq/kg), kidney (0.28–0.32 mg ai eq/kg), and muscle (0.11–0.15 mg ai eq/kg). Radioactive residues in perirenal and omental fat averaged 0.091-0.43 mg ai eq/kg in the two animals.

In a supplementary study, one lactating goat was orally dosed for 7 days with 10 ppm ^{14}C-fosetyl-Al in the diet (20 mg/day). Milk, urine and faeces were collected daily and respired air was collected using a mask covering the goat's mouth and nose, with 3-minute collections taken at 30–60 minute intervals.

In expired air, $^{14}CO_2$ was not detected within the first 30 minutes but reached a maximum about 1.5–2 hours after each dosing and slowly declined to near background within 24 hours, with total residues being about 5.7% of the administered dose

In milk, residues reached a plateau after 3 days (0.27–0.3 mg ai eq/kg) and in total, made up 2% of the administered dose. Milk samples (containing 2.2 mg ai eq/kg fosetyl-Al) were fractionated into casein (milk proteins) and extracted with petroleum ether. Radioactive residues in the petroleum ether fraction were 82% TRR with 10% TRR in the aqueous fraction and 9.3% in the precipitated protein fraction.

In a third study where lactating goats (2) were dosed orally by capsule, morning and evening for 7 consecutive days with ^{14}C-fosetyl-Al at doses equivalent to 27.8 ppm and 30 ppm in the diet, the animals were sacrificed 14–16 hours after the 7th daily dose and various tissue samples were taken for extraction and analysis.

About 11% of the administered dose was excreted in urine and 5.5–8.4% in faeces. In milk, there was a gradual increase of the radioactivity levels, reaching a plateau after 3–4 days, with total residues making up about 14–16% of the total administered dose.

In tissues, radioactive residues were < 5% of the administered dose, measured in liver at about 2.4 mg ai eq/kg) and in kidney at 1.0–1.4 mg ai eq/kg. Radioactive residues in fat were 0.76–1.5 mg ai eq/kg and in muscle were 0.45–0.53 mg ai eq/kg. The total recovery of radioactive residues in expired air (CO_2) during a 10-hour collection starting just after the morning dose on the 6th day was used to calculate a total contribution of 14–15% of the administered dose.

Residues of ^{14}C-fosetyl-Al and ^{14}C-ethanol were only found in the urine and stomach contents. In milk and edible tissues all ^{14}C-residues were characterised as natural products (carbohydrates and carboxylic acids, glycogen, saponifiable fatty acids (about 42% TRR in milk) and lipids, as well as amino acids and peptides).

The proposed fosetyl-Al metabolic pathway in animals involves dissociation and conversion of fosetyl via O-ethyl phosphonic acid to ethanol and phosphonic acid. The ethanol is oxidized to acetic acid, which is then incorporated into natural products or exhaled as CO_2.

Phosphonic acid

No information was available on the metabolism of phosphonic acid in animals, but the Meeting noted that inorganic phosphites are generally considered to be biologically inert in animals and are rapidly excreted. In a rat study using ^{32}P-phosphonate, around 30% of labelled material was excreted in faeces in the form of phosphonate or phosphate. Overall, conversion of phosphonate to phosphate was around 10% of the administered dose.

Methods of analysis

Analytical methods have been reported and validated for the analysis of fosetyl-Al (and fosetyl) and for phosphonic acid in plant and animal commodities. These methods are based on either those involving GC analysis after a derivatisation step (methylation) or those involving LC-MS/MS analysis.

Data generation methods for plant and animal commodities, based on the methylation of fosetyl-Al (and fosetyl) to methyl ethylphosphonate and phosphonic acid to dimethylphosphonate, generally involve extraction with either water, sulphuric acid or HCl/ACN, followed by either centrifugation and filtration or cartridge or column clean-up. Extracts are then diluted with isopropanol and residues are derivatised with diazomethane or TMSD. The methylated residues are then analysed by GC-FPD or GC-NPD with external standards. LOQs for fosetyl-Al range from 0.05–0.5 mg/kg (up to 5.0 mg/kg in hops). The LOQs for phosphonic acid ranged from 0.1–0.5 mg/kg (up to 20 mg/kg in hops).

The more recent LC-MS/MS methods for data generation (plant and animal commodities) also generally involve extraction with either water/ACN, sulphuric acid or HCl/ACN, followed by either centrifugation and filtration or cartridge or column clean-up, with analysis by LC-MS/MS. LOQs for fosetyl-Al were generally 0.01 mg/kg (0.05 mg/kg in pineapple and animal tissues, 1.0 mg/kg in hops). The LOQs for phosphonic acid ranged from 0.01 (milk) to 0.2 mg/kg (0.5 mg/kg in pineapple and up to 20 mg/kg in hops).

In addition to the above LC-MS/MS methods, the multi-residue QuPPe method is suitable for the analysis of fosetyl-Al and phosphonic acid in representative samples with a high water, high oil, high protein, high starch and high acid content. This method involves extraction in acidified methanol, centrifugation and dilution prior to LC-MS/MS analysis. LOQs are 0.01 mg/kg (fosetyl-Al) and 0.1 mg/kg (phosphonic acid).

The Meeting concluded that suitable data generation methods are available to measure fosetyl-Al, fosetyl and phosphonic acid in plant and animal commodities and the QuPPe multi-residue method is suitable for monitoring residues of these analytes in most plant commodities.

Stability of pesticide residues in stored analytical samples

The stability of fosetyl-Al and phosphonic acid residues in frozen stored analytical samples was investigated in a range of plant commodities with high water content, high acid content, high oil content and high starch/protein content.

While fosetyl-Al residues were not stable in high water content and high oil commodities and residue stability was variable in high acid commodities (with residues hydrolysing to phosphonic acid), in the storage stability studies where both fosetyl-Al and phosphonic acid residue degradation was measured, the total residues of fosetyl-Al and phosphonic acid were stable over the storage intervals in the studies (6–25 months for high water content, high starch/protein content, high acid content and 29 months for high oil content.

Definition of the residue

Plant commodities

Plant metabolism and environmental fate studies show that following the use of fosetyl and its aluminium salt (fosetyl-Al), residues are readily and rapidly hydrolysed to phosphonic acid and

ethanol in plants and soil. Phosphonic acid is the predominant metabolite, generally making up more than 80% of the total residue, with fosetyl or fosetyl-Al also present in food commodities from treated crops. The ethanol metabolite is either volatilized or degraded and incorporated in natural constituents of plant and animal tissues.

Following the use of phosphonic acid (as the ammonium, potassium, sodium salts), residues are also rapidly absorbed and translocated, accumulating in sink organs.

Although analytical methods are available for measuring fosetyl/fosetyl-Al and phosphonic acid separately, as either the individual compounds or their methylated derivatives, storage stability studies show that in a number of commodities fosetyl/fosetyl-Al can degrade to phosphonic acid in frozen analytical samples.

The Meeting therefore considered that establishing separate residue definitions for fosetyl/fosetyl-Al and phosphonic acid (and it salts) would not be appropriate and agreed to consider a single residue definition based on the combined residues of fosetyl/fosetyl-Al and phosphonic acid, expressed as phosphonic acid.

Phosphonic acid, as the major metabolite of fosetyl-Al, and fosetyl are toxicologically similar to fosetyl-Al and are covered by the ADI for fosetyl-Al.

The proposed residue definition for plant commodities, for both MRL-compliance and for dietary exposure estimation is "Sum of fosetyl, phosphonic acid and their salts, expressed as phosphonic acid".

Animal commodities

The animal metabolism studies indicate that the behaviour of fosetyl/fosetyl-Al in animals is similar to that in plants, with residues being rapidly metabolised to phosphonic acid and to ethanol which in turn is incorporated into natural products.

For fosetyl-Al, the results of the 7-day goat metabolism study and the 28-day dairy cow and poultry feeding studies show that residues of intact fosetyl-Al or fosetyl are not expected in milk, eggs or any tissues from animals dosed with 10 ppm (dairy cows), 20 ppm (poultry) and 30 ppm (goat) in the diet.

For phosphonic acid, the 28-day dairy cow feeding study indicates that measurable residues can be found in kidney (0.55 mg/kg) and detectable residues could be expected in fat and liver (about 0.2 mg/kg) and also in muscle (0.02 mg/kg) following dosing with 94 ppm in the diet. Residues were not detected in milk or in eggs and poultry tissues from hens exposed to 265 ppm phosphonic acid in the diet.

Based on the above, the Meeting considered that only phosphonic acid residues could be expected in tissues, milk or eggs from animals exposed to feed commodities from crops treated with fosetyl/fosetyl-Al or phosphonic acid or its salts.

The proposed residue definition for animal commodities is "phosphonic acid and its salts, expressed as phosphonic acid', for both MRL-compliance and for dietary exposure estimation.

The Meeting noted that multi-residue methods exists to measure fosetyl-Al, fosetyl and phosphonic acid residues in plant and animal commodities and based on the chemical properties of phosphonic acid the Meeting concluded that the residue is not fat soluble.

Proposed definition of the residue for compliance with the MRL and for estimation of dietary exposure for plant commodities: *"Sum of fosetyl, phosphonic acid and their salts, expressed as phosphonic acid"*

Proposed definition of the residue for compliance with the MRL and for estimation of dietary exposure for animal commodities: *"Phosphonic acid"*

The residue is not fat-soluble.

Results of supervised residue trials on crops

The Meeting received GAP information and supporting residue information for fosetyl-Al on citrus, pome fruit, grapes, strawberries, avocado, pineapple, cucurbits, other fruiting vegetables, leafy vegetables and hops; for fosetyl on tomatoes, peppers and spinach and for phosphonic acid on citrus, grapes and tree nuts.

In this Appraisal, the term 'total residues' is used to describe the sum of the phosphonic acid residues and the fosetyl/fosetyl-Al residues (expressed as phosphonic acid) and the Meeting agreed to use the following formulae to calculate these total residues:

Fosety-Al

$$\text{Total residue [mg/kg]} = \frac{\text{fosetyl-Al [mg/kg]} \times MW_{\text{phosphonic acid}} \times 3}{MW_{\text{fosetyl-Al}}} + \text{phosphonic acid [mg/kg]}$$

Fosetyl

$$\text{Total residue [mg/kg]} = \frac{\text{fosetyl [mg/kg]} \times MW_{\text{phosphonic acid}}}{MW_{\text{fosetyl}}} + \text{phosphonic acid [mg/kg]}$$

$MW_{\text{fosetyl-Al}}$: Molecular weight of fosetyl-Al = 354.1 g/mol

$MW_{\text{phosphonic acid}}$: Molecular weight of phosphonic acid = 82 g/mol

MW_{fosetyl}: Molecular weight of fosetyl = 110 g/mol

Conversion factors are 0.695 (fosetyl-Al to phosphonic acid) and 0.745 (fosetyl to phosphonic acid).

In many trials, residues of phosphonic acid (and to a lesser extent fosetyl and fosetyl-Al) were measured in control samples. The Meeting agreed that where these residues were less than 20% of the concentrations reported in the treated samples, the values could be used for maximum residue level estimation.

Supervised residue trials from USA on citrus, pome fruit, grapes, strawberries, avocados, cucumber, summer squash, melons, tomatoes, lettuce, spinach and hops were provided to the Meeting. However, since these trials only reported residues of fosetyl-Al but not phosphonic acid, the Meeting was not able to use these data.

Citrus fruits

Mandarin - Fosetyl-Al

The GAP for fosetyl-Al on citrus in USA is for up to 4 foliar sprays of up to 4.48 kg ai/ha, with a PHI of 12 hours.

In trials conducted in Europe on mandarin, matching the GAP in USA but with a higher application rate of 7 kg ai/ha, total residues were (n=9): 7.8, 14, 21, 21, 21, 23, 28, 39 and 39 mg/kg.

When scaled to the USA GAP application rate (4.48/7.0), total residues are (n=9): 5.0, 9.0, 13, 13, 13, 15, 18, 25 and 25 mg/kg.

The Meeting estimated an STMR of 13 mg/kg and a maximum residue level of 50 mg/kg for the sub-group of mandarins

Orange - Fosetyl-Al

In trials in conducted in Europe on orange, matching the GAP in USA for citrus (4 foliar sprays of 4.48 kg ai/ha, PHI of 12 hours) but with a higher application rate of 7 kg ai/ha, total residues were: 5.6, 6.7, 6.9, 6.9, 7.5, 7.8, 8.9, 10 and 14 mg/kg.

When scaled to the USA GAP application rate (4.48/7.0), total residues are (n=9): 3.6, 4.3, 4.4, 4.4, 4.8, 5.0, 5.7, 6.4 and 9.0 mg/kg.

The Meeting estimated an STMR of 4.8 mg/kg and a maximum residue level of 20 mg/kg for the sub-group of oranges

Citrus fruit - Phosphonic acid

In USA, the post-harvest GAP for phosphonic acid on citrus is as a dip, drench or an in-line spray of 1.8 kg ai/hL. No trials matching this GAP were available and although trials involving application rates of 0.6 kg ai/hL were available, the Meeting noted that the proportionality approach was not yet validated for post-harvest treatments.

GAP in the USA for foliar applications is 6.76 kg ai/ha, usually applied in March/April, May/June and September/October, with an application made 2-4 weeks before harvest for post-harvest mould suppression, but with no defined PHI. No trials matching this GAP were available.

Pome fruits

Apples, pears - Fosetyl-Al

GAP for fosetyl-Al on apples and pears in Greece is for up to 4 foliar sprays of 0.2 kg ai/hL, up to 4.0 kg ai/ha, 3-day PHI. No supervised field trials were available matching this GAP.

The critical GAP in France for fosetyl-Al on pome fruit is 3 foliar applications of 3.0 kg ai/ha, 28-day PHI. In European trials matching this GAP, total residues in apples were (n=7): 7.6, 8.2, 11, 12, 16, 17, and 22 mg/kg and in pears, were (n=8): 12, 13, 14, 15, 15, 15, 17 and 17 mg/kg

Since the Mann-Whitney test indicated that the data sets for apples and pears were not statistically different, the Meeting agreed to combine them to estimate a group maximum residue level for pome fruit. The combined data set is (n=15): 7.6, 8.2, 11, 12, 12, 13, 14, 15, 15, 15, 16, 17, 17, 17 and 22 mg/kg.

The Meeting estimated an STMR of 15 mg/kg and a maximum residue level of 50 mg/kg for pome fruit.

Berries and small fruit

Grapes - Fosetyl-Al

GAP for fosetyl-Al on grapes in Denmark is for up to 6 foliar sprays of 0.2 kg ai/hL, 35-day PHI and the GAP in Greece is for up to 4 foliar applications of 0.2 kg ai/hL, 3.6 kg ai/ha, 14-day PHI. No supervised field trials were available matching these GAPs.

GAP for fosetyl-Al on grapes in Brazil is up to 3 foliar applications of 0.2 kg ai/hL, 15-day PHI. In Brazilian trials matching this GAP, total residues were: 17, 41 and 56 mg/kg.

The critical GAP in the Czech Republic for fosetyl-Al on grapes is for up to 3 foliar applications of 2.0 kg ai/ha, 21-day PHI. In European trials matching this GAP, total residues were (n=22): 4.7, 8.0, 10, 11, 12, 12, 12, 13, 14, 14, 15, 16, 19, 20, 24, 24, 27, 28, 32, 32, 37, 40 mg/kg.

The Meeting estimated an STMR of 15.5 mg/kg and a maximum residue level of 60 mg/kg for grapes.

Grapes - Phosphonic acid

GAP for phosphonic acid on grapes in Australia is 2.4 kg ai/ha, with no reference to a maximum number of applications or to a PHI.

In the residue trials from Australia, treatments ranged from 1–6 applications of 1.0–3.0 kg ai/ha, with intervals to harvest ranging from 5 days to about 18 weeks. In trials involving 4 applications of 2.4 kg ai/ha, phosphonic acid residues in grapes sampled 5–8 days after the last

treatment were: 47, 67, 67 and 102 mg/kg. The Meeting agreed that these data were not sufficient to estimate a maximum residue level for phosphonic acid on grapes.

Strawberries - Fosetyl-Al

GAP for fosetyl-Al on strawberries in France is up to 3 foliar applications of 4.0 kg ai/ha, 14-day PHI. In European indoor strawberry trials matching this GAP, total residues were: 9.5, 9.5, 10, 10, 11, 18, 26, 34 mg/kg.

In European outdoor strawberry trials matching the GAP in France, total residues were: 4.3, 5.1, 6.7, 11, 11, 24, 36, 44 mg/kg

Since the Mann-Whitney test indicated that the data sets for indoor and outdoor strawberries were not statistically different, the Meeting agreed to combine these data sets to estimate a maximum residue level. The combined data set is (n=16): 4.3, 5.1, 6.7, 9.5, 9.5, 10, 10, 11, 11, 11, 18, 24, 26, 34, 36, 44 mg/kg

The Meeting estimated an STMR of 11 mg/kg and a maximum residue level of 70 mg/kg for strawberries.

Assorted tropical and subtropical fruit – inedible peel

Avocado – fosetyl-Al

GAP for fosetyl-Al on avocados in Spain is for up to 3 foliar applications of 0.24 kg ai/hL, 14-day PHI and 5 trials conducted in Spain were available.

In one trial matching the GAP in Spain, total residues in whole fruit were 3.2 mg/kg and in flesh were 3.4 mg/kg

In three trials matching the GAP in Spain but with higher application rates of 0.31–0.34 kg ai/hL, total residues in whole fruit were 3.5, 3.8 and 4.8 mg/kg and in flesh were 2.8, 4.0 and 7.8 mg ai/kg.

In one trial matching the GAP in Spain but with a higher application rate of 0.46 kg ai/ha, total residues in whole fruit were 20 mg/kg and in flesh were 35 mg/kg

When proportionally adjusted to match the GAP in Spain, scaled total residues in whole fruit are (n=5): 2.7, 2.7, 3.2, 3.4 and 10 mg/kg and in flesh, are (n=5): 2.0, 2.8, 3.4, 6.0 and 18 mg/kg in flesh.

The Meeting estimated an STMR of 3.4 mg/kg (in flesh) and a maximum residue level of 20 mg/kg for avocado.

Pineapple – fosetyl-Al

GAP for pineapples in USA is for a pre-plant dip (0.24 kg ai/hL) followed by up to 6 foliar applications of 0.36 kg ai/hL, 90-day PHI. In trials conducted in USA matching this GAP but with lower foliar application rates of 0.24 kg ai/hL, total residues were: 1.0, 3.1 and 8.2 mg/kg

When proportionally adjusted to match the USA GAP foliar application rate, scaled total residues are: 1.5, 4.7 and 12 mg/kg.

GAP for pineapples in Brazil is for a pre-plant dip (0.08 kg ai/hL) and up to 3 foliar applications of 0.2 kg ai/hL, 20-day PHI. No trials matching this GAP were available.

The Meeting concluded there were insufficient data to estimate a maximum residue level for pineapple.

Fruiting vegetables, Cucurbits

Cucumber – fosetyl-Al

The GAP for cucumbers in Greece is for up to 4 foliar applications of 4.8 kg ai/ha, 1-day PHI. In protected cucumber trials conducted in Europe matching this GAP, total residues were (n=7): 6.8, 11, 13, 14, 14, 21 and 38 mg/kg.

The Meeting estimated an STMR of 14 mg/kg and a maximum residue level of 60 mg/kg for cucumber.

Summer Squash – fosetyl-Al

The GAP for summer squash in Greece is for up to 4 foliar applications of 4.8 kg ai/ha, 3-day PHI. In summer squash trials conducted in Europe matching this GAP but involving lower application rates (3.2 kg ai/ha), residues were: 8.1, 11, 16, 18, 19 and 19 mg/kg.

When proportionally adjusted to match the GAP in Greece, scaled residues (4.8/3.2) are (n=6): 12, 17, 24, 27, 29 and 29 mg/kg.

The Meeting estimated an STMR of 25.5 mg/kg and a maximum residue level of 70 mg/kg for summer squash.

Melons – fosetyl-Al

The GAP for melons in Greece is for up to 4 foliar applications of 4.8 kg ai/ha, 3-day PHI. No supervised field trials were available matching this GAP.

The GAP for melons in France is for up to 2 foliar applications of 3.2 kg ai/ha, 3-day PHI. In protected melon trials conducted in Europe matching this GAP, total residues in whole fruit were (n=8): 5.8, 12, 14, 14, 17, 19, 21 and 28 mg/kg and in flesh, were (n=8): 11, 12, 14, 14, 18, 18, 19 and 21 mg/kg.

In outdoor melon trials conducted in Europe matching the GAP in France, total residues in whole fruit were (n=6): 12, 12, 20, 22, 25 and 29 mg/kg and in flesh, were (n=6): 9.2, 9.7, 12, 14, 16 and 24 mg/kg.

Since the Mann-Whitney test indicated that the data sets for indoor and outdoor melons were not statistically different, the Meeting agreed to combine these data sets to estimate a maximum residue level. For whole fruit, the combined data set is (n=14): 5.8, 12, 12, 12, 14, 14, 17, 19, 20, 21, 22, 25, 28 and 29 mg/kg. For flesh, the combined data set is (n=14): 9.2, 9.7, 11, 12, 12, 14, 14, 14, 16, 18, 18, 19, 21 and 24 mg/kg

The Meeting estimated an STMR of 14 mg/kg (in flesh) and a maximum residue level of 60 mg/kg for melons (except water melon).

Fruiting vegetables, other than Cucurbits

Peppers – fosetyl

The GAP for outdoor sweet peppers in France is for up to 2 seedling drench treatments prior to planting out, the first at the equivalent of 18.6 kg ai/ha and the second equivalent to 9.3 kg ai/ha, with these being followed by up to 2 drip irrigation treatments of 0.93 kg ai/ha, 3-day PHI. In outdoor sweet pepper trials conducted in Europe matching this GAP, total residues were (n=9): < 0.21 (4), 0.21, 0.21, 0.29, 0.72 and 0.75 mg/kg.

The GAP for indoor peppers in Hungary is for up to 2 seedling drench treatments prior to planting out, the first at the equivalent of 18.6 kg ai/ha and the second equivalent to 9.3 kg ai/ha, with these being followed by up to 4 drip irrigation treatments of 0.93 kg ai/ha, 3-day PHI. In indoor sweet pepper trials conducted in Europe matching this GAP, total residues were (n=9): < 0.21, 0.21, 0.22, 0.31, 0.36, 0.54, 2.4, 3.1 and 3.5 mg/kg.

Based on the data supporting the GAP for indoor peppers, the Meeting estimated an STMR of 0.36 mg/kg and a maximum residue level of 7 mg/kg for peppers, sweet.

Tomato - fosetyl

The GAP for outdoor tomatoes in France is for up to 2 seedling drench treatments (equivalent to 9.3 kg ai/ha) prior to planting out, followed by up to 2 drip irrigation treatments of 0.93 kg ai/ha, 3-day PHI. In outdoor tomato trials conducted in Europe matching this GAP, total residues were: < 0.21 (10), 0.27, 0.44, 0.51, 1.0 and 1.0 mg/kg.

The GAP for indoor tomatoes in Hungary is for up to 2 seedling drench treatments (equivalent to 9.3 kg ai/ha) prior to planting out, followed followed by up to 4 drip irrigation treatments of 0.93 kg ai/ha, 3-day PHI. In indoor tomato trials conducted in Europe matching this GAP, total residues were (n=8): 0.21, 0.24, < 0.34, 0.34, 0.34, 0.36, 0.47 and 5.2 mg/kg.

Based on the data supporting the GAP for indoor tomatoes, the Meeting estimated an STMR of 0.34 mg/kg and a maximum residue level of 8 mg/kg for tomato.

Leafy vegetables

Lettuce – fosetyl-Al

The GAP for lettuce in Finland is for foliar applications of 2.4 kg ai/ha, 14-day PHI.

In indoor leaf lettuce trials conducted in Europe matching this GAP, with 4 applications of fosetyl-Al, total residues were (n=8): 7.7, 7.8, 9.2, 13, 15, 17, 27 and 31 mg/kg.

In outdoor leaf lettuce trials conducted in Europe matching this GAP, with 4 applications of fosetyl-Al, total residues were (n=10): 4.8, 6.9, 7.1, 8.1, 8.2, 8.5, 9.0, 15, 15 and 16 mg/kg.

Since the Mann-Whitney test indicated that the data sets for indoor and outdoor leaf lettuce were not statistically different, the Meeting agreed to combine these data sets to estimate a maximum residue level. For leaf lettuce, the combined data set is (n=18): 4.8, 6.9, 7.1, 7.7, 7.8, 8.1, 8.2, 8.5, 9.0, 9.2, 13, 15, 15, 15, 16, 17, 27 and 31 mg/kg.

The Meeting estimated an STMR of 9.1 mg/kg and a maximum residue level of 40 mg/kg for leaf lettuce.

In indoor head lettuce trials conducted in Europe matching the GAP for lettuce in Finland (2.4 kg ai/ha, PHI of 14 days), with 4 applications of fosetyl-Al, total residues were (n=7): 12, 19, 36, 41, 57, 66 and 120 mg/kg.

Based on the data supporting the GAP for indoor head lettuce, the Meeting estimated an STMR of 41 mg/kg and a maximum residue level of 200 mg/kg for lettuce.

Spinach - fosetyl

The critical GAP for fosetyl on spinach in Belgium is on outdoor crops, one foliar application of 0.775 kg ai/ha, with a 14-day PHI on outdoor crops. In outdoor spinach trials conducted in Europe matching this GAP, total residues were (n=8): 0.53, 0.79, 2.4, 4.0, 4.2, 5.3, 6.5, 11 mg/kg.

The Meeting estimated an STMR of 4.1 mg/kg and a maximum residue level of 20 mg/kg for spinach.

Tree nuts

Almond, pistachio, walnut – phosphonic acid

The GAP for tree nuts in USA is for up to 6 foliar applications of 1.9 kg ai/ha, with no specified PHI.

In trials conducted in USA and matching this GAP (with PHI of 1-4 days), phosphonic acid residues in almond nutmeat were (n=5): < 0.5, < 0.5, 0.51, 5.6 and 100 mg/kg, in pistachio nutmeat,

residues were (n=5) 1.8, 65, 167, 169 and 197 mg/kg and in walnut nutmeat, were (n=5): 3.8, 38, 54, 67 and 172 mg/kg.

Since the Kruskall-Wallis test indicated that the data sets for almonds, pistachios and walnuts were not statistically different, the Meeting agreed to combine these data sets to estimate a maximum residue level for tree nuts. The combined data set is (n=15): < 0.5, < 0.5, 0.51, 1.8, 3.8, 5.6, 38, 54, 65, 67, 100, 167, 169, 172 and 197 mg/kg.

The Meeting estimated an STMR of 54 mg/kg and a maximum residue level of 400 mg/kg for tree nuts.

Dried herbs

Hops (dry) – fosetyl-Al

The GAP for fosetyl-Al in Germany is for up to 8 foliar applications of 8.0 kg ai/ha, 14-day PHI. In trials conducted in Europe matching this GAP, total residues in dried cones were (n=6): 309, 322, 325, 376, 404 and 660 mg/kg.

The Meeting estimated an STMR of 350 mg/kg and a maximum residue level of 1500 mg/kg for hops (dry).

Fate of residues during processing

Both fosetyl-Al and phosphonic acid are stable to hydrolysis under conditions simulating pasteurisation, baking, brewing, boiling and sterilization.

The fate of fosetyl-Al, fosetyl and phosphonic acid residues has been examined in a number of studies simulating household processing involving peeling (citrus, avocado, pineapple and melon), washing (lettuce), cooking (spinach, green beans) and commercial processing of oranges, apples, grapes, strawberries, tomatoes, peppers, lettuce, spinach, beans and hops.

Following the use of fosetyl/fosetyl-Al, total residues increased in tomato puree and in grape pomace and dry citrus pomace. Following the use of phosphonic acid, residues increased in wine and citrus pomace.

For the commodities considered at the Meeting, estimated processing factors and STMR-Ps for their processed food or feed commodities are summarised below.

RAC [STMR]	Matrix	Calculated processing factors	PF (median or best fit)	STMR-P (mg/kg)
Fosetyl-Al [a]				
Orange [4.8 mg/kg]	juice pomace (dry)	0.35, 0.57, 0.94, 1.1, 1.4 0.45, 0.77, 3.4, 3.9, 4.6	0.94 3.4	4.5 16
Apple [15 mg/kg]	juice wet pomace puree	0.63, 1.2 0.49, 1.6 0.44, 0.71, 1.1	0.92 1.0 0.71	14 15 11
Grapes [15.5 mg/kg]	juice must wet pomace wine	0.5, 0.69, 0.94, 0.96, 1.1, 1.2, 1.2 0.06, 0.17, 0.34, 0.39, 0.59, 0.62, 0.77, 0.84, 1.4 0.59, 1.3, 1.4, 2.4 0.11, 0.35, 0.43, 0.51, 0.52, 0.55, 0.63, 0.64,0.7, 0.77, 0.84, 1.1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.8, 2.4	0.96 0.59 1.4 0.77	15 9.1 22 12
Strawberry [11 mg/kg]	washed jam canned	0.89, 1.0 0.52, 0.5 0.62, 0.4	0.95 0.51 0.51	11 5.6 5.6
Hops [350 mg/kg]	Beer	0.0022, 0.0031, 0.0045, 0.0048, 0.0049, 0.0055, 0.0055, 0.0064, 0.018	0.0049	1.7

RAC [STMR]	Matrix	Calculated processing factors	PF (median or best fit)	STMR-P (mg/kg)
Fosetyl [a]				
Tomato [0.34 mg/kg]	washed	0.75, 1.0	0.88	0.3
	juice	0.75, 0.83	0.79	0.27
	puree	1.3, 1.5	1.4	0.48
	preserve	0.87, 0.91	0.89	0.3
	wet pomace	1.1, 1.1	1.1	0.37
Spinach [4.1 mg/kg]	washed	0.73, 0.86, 1.2, 1.2	1.0	4.1
	cooked	0.66, 0.91, 0.95, 1.0	0.93	3.8

[a] The processing factor is the ratio of total residues in the processed item divided by the total residue in the RAC.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of fosetyl, phosphonic acid and their salts (expressed as phosphonic acid) in farm animals on the basis of the diets (US/CAN, EU, Australia and Japan) listed in OECD Feed Table 2013.

	Animal dietary burden, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	1.8	1.8	7.5	7.5	31[a]	31[c]	-	-
Dairy cattle	3.8	3.8	5.5	5.5	31[b]	31[d]	-	-
Poultry – broiler	-	-	-	-	-	-	-	-
Poultry – layer	-	-	-	-	-	-	-	-

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

[b] Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk

[c] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian tissues.

[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

Farm animal feeding studies

Lactating dairy cows – fosetyl-Al + phosphonic acid

In a lactating dairy cow feeding study, groups of 3 cows were dosed orally twice a day (after each milking) for 28 days with a 1:10 mixture of fosetyl-Al and disodium phosphonate (in gelatine capsules) at rates equivalent to 11 ppm, 32 ppm and 100 ppm phosphonic acid equivalents respectively.

No intact fosetyl-Al or fosetyl residues were detected in any of the tissues or milk analysed except in one sample of liver from the 32 ppm dose group, where a residue of 0.081 mg/kg (<LOQ) was detected. Phosphonic acid residues were detected at all three dose levels, estimated at up to 0.16 mg/kg in liver, 0.2 mg/kg in fat, 0.06 mg/kg in milk in the 100 ppm dose group and 0.02–0.09 mg/kg in muscle. Highest residues were in kidney (up to 0.6 mg/kg), reflecting the urinary route of elimination. In the 32 ppm dose group, estimated mean total residues were 0.29 mg/kg (kidney), 0.22 mg/kg (liver), 0.12 mg/kg (fat), 0.07 mg/kg (muscle) and 0.05 mg/kg in milk, with maximum residues in individual animals being 0.3 mg/kg (kidney), 0.33 mg/kg (liver), 0.18 mg/kg (fat) and 0.086 mg/kg (muscle).

Poultry – fosetyl-Al + phosphonic acid

In a poultry feeding study, three groups of ten hens were dosed for 28 days with a 1:9 mixture of fosetyl-Al:disodium phosphonate incorporated into their diet. Dose rates were equivalent 14 ppm, 42 ppm and 142 ppm phosphonic acid equivalents.

All eggs were collected and pooled to obtain a single sample from each dose group and pooled eggs from each dose group were also sampled at intervals throughout the dosing period. On day 28 the hens were sacrificed and breast and thigh muscle, liver and abdominal fat were sampled and stored frozen for less than 28 days before analysis.

No residues of either intact fosetyl-Al, intact fosetyl or phosphonic acid were detected in any tissue samples with trace levels of phosphonic acid (estimated at up to 0.2 mg/kg phosphonic acid) found in eggs from some hens in all dose groups.

Animal commodity maximum residue levels

Cattle

The Meeting noted that the maximum and mean cattle dietary burden of 31 ppm was approximately the same as the 32 ppm dose group in the second dairy cow feeding study where mean estimated phosphonic acid equivalent residues were 0.29 mg/kg (kidney), 0.22 mg/kg (liver), 0.12 mg/kg (fat), 0.07 mg/kg (muscle) and 0.05 mg/kg in milk.

The Meeting estimated maximum residue levels of 0.15 mg/kg for meat (from mammals other than marine mammals), 0.5 mg/kg for edible offal (mammalian) and 0.2 mg/kg for mammalian fat and a maximum residue level of 0.1 mg/kg for milks.

Estimated STMRs are 0.29 mg/kg (kidney), 0.22 mg/kg (liver), 0.12 mg/kg (fat), 0.07 mg/kg (muscle) and 0.05 mg/kg for milks.

Poultry

As there were no poultry feed commodities from the treated crops, the Meeting agreed not to estimate maximum residue levels for poultry commodities.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI assessment.

Definition of the residue (for compliance with the MRL and for the estimation of dietary exposure) for plant commodities: *Sum of fosetyl, phosphonic acid and their salts, expressed as phosphonic acid*.

Definition of the residue (for compliance with the MRL and for the estimation of dietary exposure) for animal commodities: *Phosphonic acid*.

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term exposure

The current Meeting established an ADI of 0–1 mg/kg bw for fosetyl-aluminium and noted that this ADI also applied to phosphonic acid.

The Meeting agreed that the International Estimated Daily Intakes (IEDIs) for fosetyl-aluminium, fosetyl and phosphonic acid could be calculated using STMRs estimated by the current

Meeting for the total residues of fosetyl, phosphorous acid and their salts (expressed as phosphonic acid).

The International Estimated Daily Intakes (IEDIs) for fosetyl, phosphorous acid and their salts were calculated for the 17 GEMS/Food cluster diets using STMRs estimated by the current Meeting for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3.

The calculated IEDIs were 1–30% of the maximum ADI of 1 mg/kg bw.

The Meeting concluded that the long-term dietary exposure to residues of fosetyl, phosphonic acid and their salts from uses considered by the current Meeting is unlikely to present a public health concern.

Short-term dietary exposure

The 2017 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term dietary exposure of residues of fosetyl, phosphonic acid and their salts is unlikely to present a public health concern.